PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Richard A. MUELLER *et al.*	)	Examiner: Robinson, B.
Serial No.: 09/625,384	)	Group Art Unit: 1625
Filed: July 26, 2000	)	Atty Dkt No.: 101765.00054

For: RETROVIRAL PROTEASE INHIBITORS

PETITION FOR EXTENSION OF RESPONSE PERIOD AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. § 1.111

U.S. Patent and Trademark Office
220 20th Street S.
Customer Window
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

In response to the Office Action dated March 29, 2004, Applicants request that the Examiner reconsider the application in view of the following remarks. Applicants petition for a two-month extension of the response period, to and including August 29, 2004, and authorize the Commissioner to charge the requisite $420 fee to our Deposit Account No. 19-0733. If this fee is incorrect, or an additional fee is required to reconsider the application in view of the following remarks, the Commissioner is authorized to charge any fee required to our Deposit Account No. 19-0733.

A Petition to the Commissioner under 37 C.F.R. § 1.181(a)(1) to withdraw the finality of the restriction requirement accompanies this response.

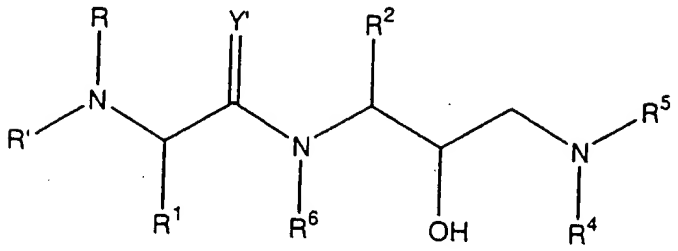
A LISTING OF CLAIMS reflects claim amendments and begins on page 2 of this paper.

A REMARKS section begins on page 46 of this paper.

LISTING OF CLAIMS

Claim 1 (withdrawn)

1. A compound represented by the formula:



(Formula I)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

R represents hydrogen, alkoxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbanoyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocycloxycarbonyl, heteroaralkoxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroarylcarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aralkylaminoalkylcarbonyl, aminoalkanoyl, aminocarbonyl, aminocarbonylalkyl, alkylaminoalkylcarbonyl, and mono- and disubstituted

aminocarbonyl and aminoalkanoyl radicals wherein the substituents are selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, alkoxycarbonyl, arylalkyloxycarbonyl, and heterocycloalkylalkyl radicals, or in the case of disubstituted aminoalkanoyl, said substituents along with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl radical;

R' represents radicals defined for R^3, or R and R' together with the nitrogen to which they are attached form a heterocycloalkyl or heteroaryl radical;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(0)NH_2$, $-C(0)NHCH_3$, $-C(0)N(CH_3)_2$, $-CH_2C(0)NHCH_3$, $-CH_2C(0)N(CH_3)_2$, alkyl, thiolalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, haloalkyl, alkoxyalkyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine, side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group

consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

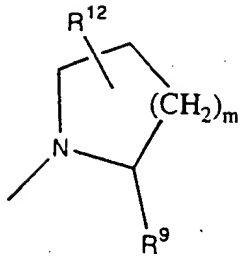
R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety; and R^6 represents hydrogen and alkyl radicals.

Claim 2 (withdrawn)

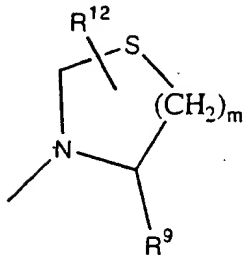
2. A compound of Claim 1 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic.

Claim 3 (withdrawn)

3. A compound of Claim 2 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



(A)



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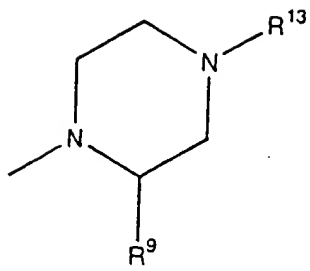
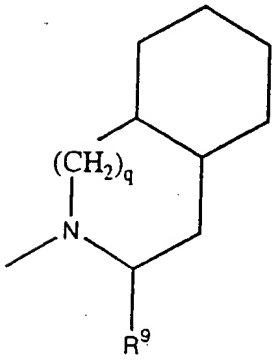
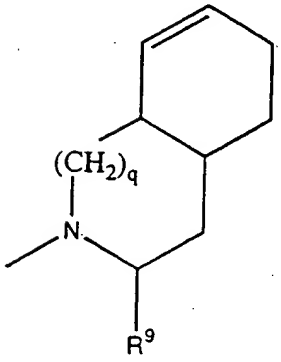


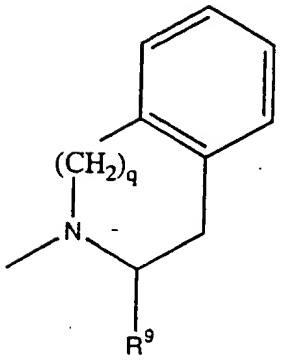
(C)



(D)



(E)



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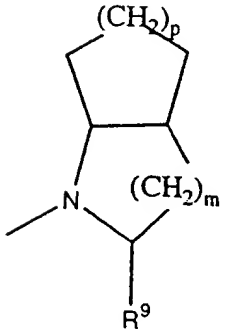
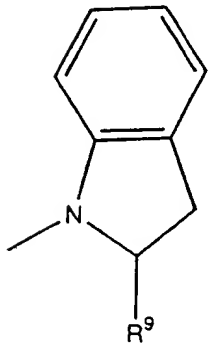
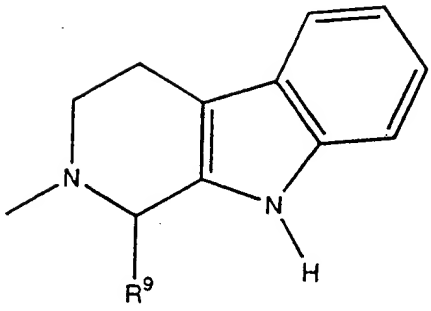


(G)



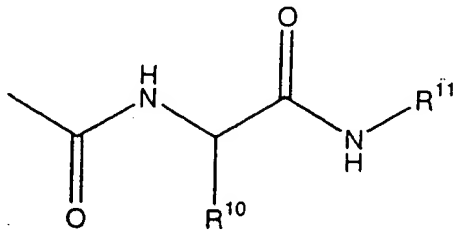
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^6 represents hydrogen and alkyl radicals.

Claim 4 (withdrawn)

4. A compound of Claim 1 where Y' is oxygen.

Claim 5 (withdrawn)

5. A compound of Claim 1 where R^2 is arylthioalkyl.

Claim 6 (withdrawn)

6. A compound of Claim 2 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

Claim 7 (withdrawn)

7. A compound of Claim 1 where R is hydrogen, alkoxycarbonyl, arylalkylcarbonyl, heterocyclecarbonyl, aminoalkanoyl, mono-substituted aminoalkanoyl, di-substituted aminoalkanoyl.

Claim 8 (withdrawn)

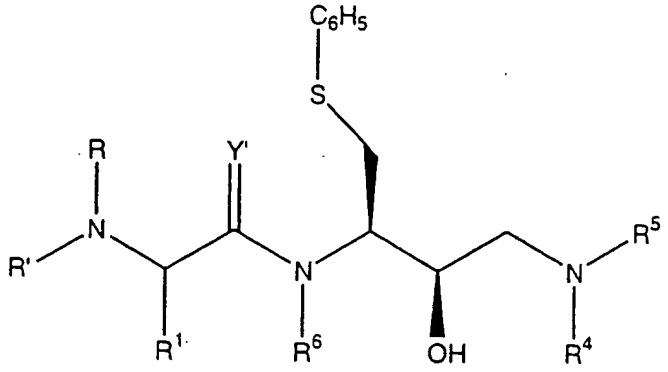
8. A compound of Claim 1 where R'is hydrogen.

Claim 9 (withdrawn)

9. A compound of Claim 3 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

Claim 10 (withdrawn)

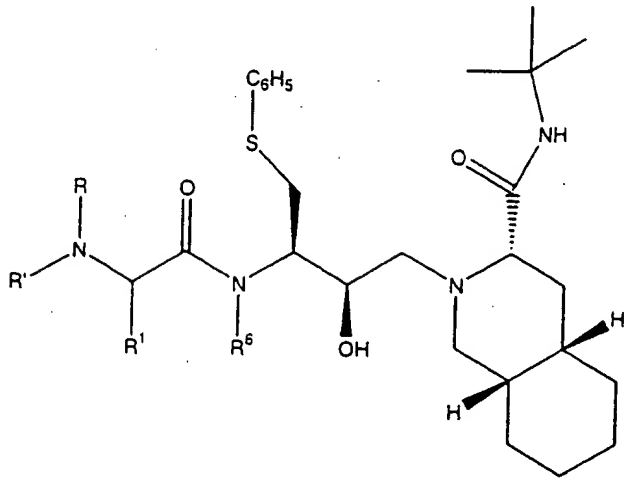
10. A compound of Claim 1 represented by the formula



wherein R, R', R^1, R^6, Y', R^4 and R^5 are as described herein.

Claim 11 (withdrawn)

11. A compound of Claim 3 represented by the formula



wherein R, R', R^1, R^6 and Y' are as described herein.

Claim 12 (withdrawn)

12. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutical carrier.

Claim 13 (withdrawn)

13. A pharmaceutical composition comprising a compound of Claim 1 and pharmaceutical carriers.

Claim 14 (withdrawn)

14. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 1.

Claim 15 (withdrawn) 15. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 1.

Claim 16 (withdrawn)

16. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 1.

Claim 17 (withdrawn)

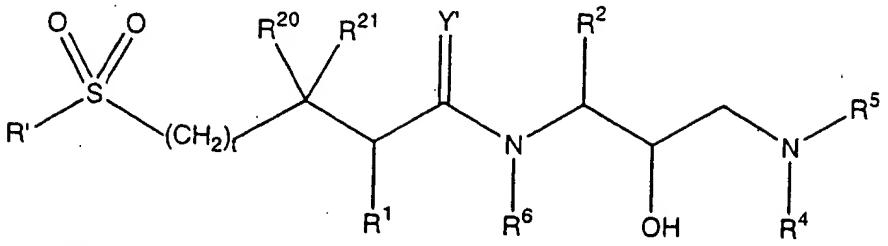
17. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 1.

Claim 18 (withdrawn)

18. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 1 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

Claim 19 (original)

19. A compound represented by the formula:



(Formula II)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

R' represents radicals defined for R';

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-CH_2C(O)NHCH_3$, $-CH_2C(O)N(CH_3)_2$, alkyl, alkylthioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, alkoxyalkyl, haloalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine,

glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocycle;

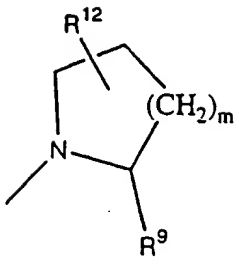
R^6 represents hydrogen and alkyl radicals;

and R^{20} and R^{21} represent radicals as defined for R^1.

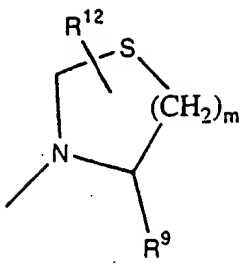
Claim 20. (original)
20. A compound of Claim 19 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11

to 16 members when tricyclic; and R^6 represents hydrogen and alkyl radicals. —

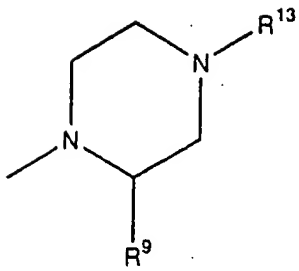
Claim 21. (original)
21. A compound of Claim 20 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



(A)



(B)



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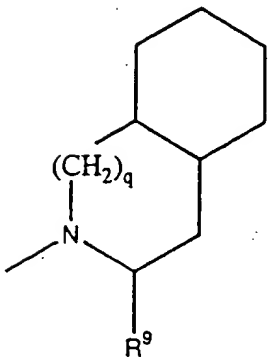
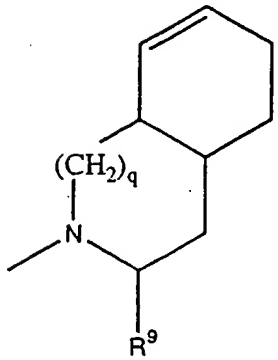


(D)



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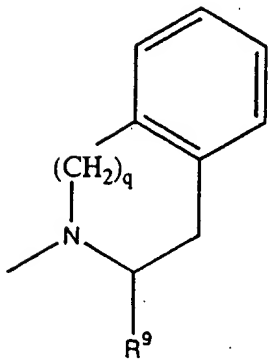

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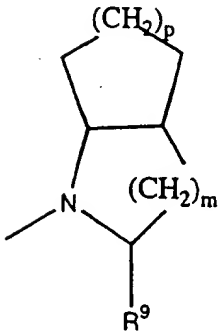
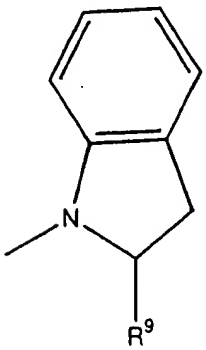
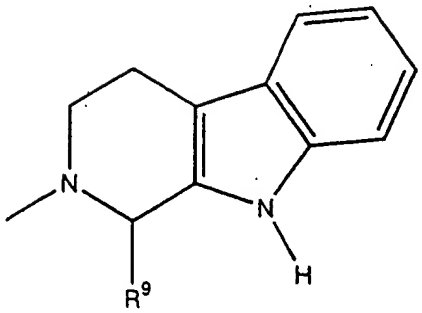


(G)



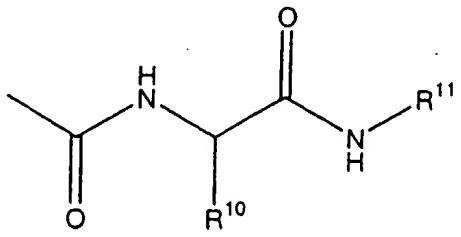
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^6 represents hydrogen and alkyl radicals.

Claim 22. (original)
22. A compound of Claim 19 where Y' is oxygen.

Claim 23. (original)
23. A compound of Claim 19 where R^2 is arylthioalkyl.

Claim 24. (original)
24. A compound of Claim 19 where t is 0.

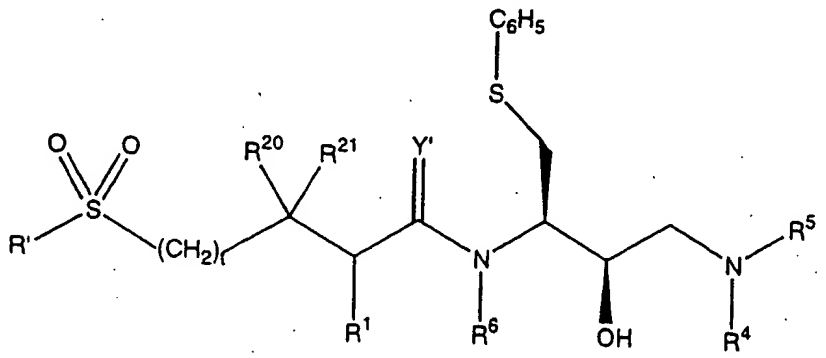
Claim 25. (original)
25. A compound of Claim 20 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

Claim 26. (original)
26. A compound of Claim 19 where R^{20} and R^{21} are hydrogen or alkyl.

Claim 27. (original)
27. A compound of Claim 19 where R'is alkyl, aryl or arylalkyl.

Claim 28. (original)
28. A compound of Claim 19 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

Claim 29. (currently amended)
29. A compound of Claim 19 represented by the Formula



wherein ~~R', R¹, R⁶, R⁴, R⁵, R²⁰, R²¹, Y' and t are as described herein.~~

R' represents radicals defined for R^3;

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-CH_2C(O)NHCH_3$, $-CH_2C(O)N(CH_3)_2$, alkyl, alkylthioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, alkoxyalkyl, haloalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

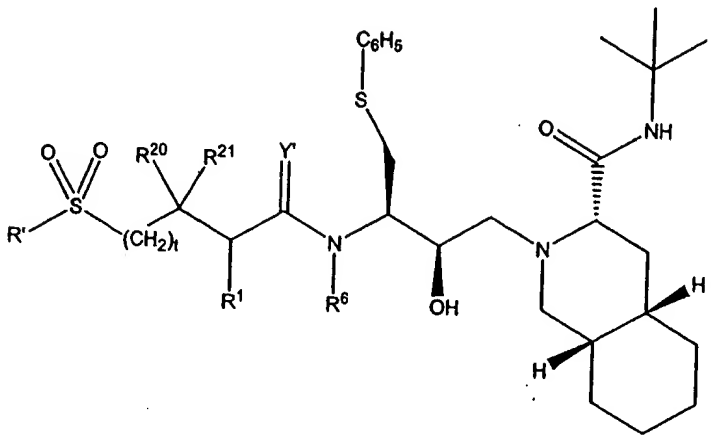
Y' represents 0, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocycle;

R^6 represents hydrogen and alkyl radicals;

and R^{20} and R^{21} represent radicals as defined for R^1.

Claim 30. (currently amended)
30. A compound of Claim 21 represented by the formula



wherein ~~R', R^1, R^6, R^4, R^5, R^{20}, R^{21}, t, and Y' are as described herein.~~

R' represents radicals defined for R^3;

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-CH_2C(O)NHCH_3$, $-CH_2C(O)N(CH_3)_2$, alkyl, alkylthioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, alkoxyalkyl, haloalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

R^6 represents hydrogen and alkyl radicals;

and R^{20} and R^{21} represent radicals as defined for R^1.

Claim 31. (original)
31. A pharmaceutical composition comprising a compound of Claim 19 and a pharmaceutical carrier.

Claim 32. (original)
32. A pharmaceutical composition comprising a compound of Claim 19 and pharmaceutical carriers.

Claim 33. (original)
33. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 19.

Claim 34. (orginal)
34. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 19.

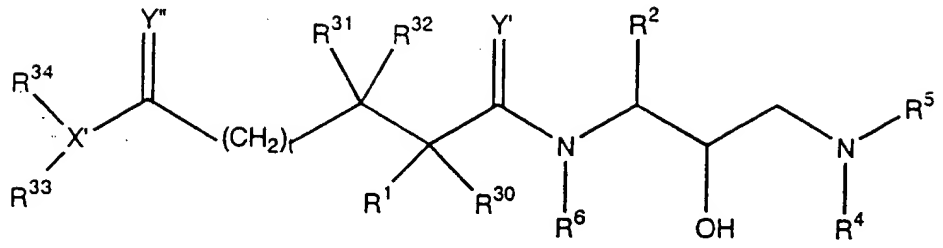
Claim 35. (original)
35. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 19.

Claim 36. (original)
36. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 19.

Claim 37. (original)
37. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 19 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

Claim 38 (withdrawn)

38. A compound represented by the formula:



(Formula III)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-CH_2C(O)NHCH_3$, $-CH_2C(O)N(CH_3)_2$, alkyl, thioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, alkoxyalkyl, haloalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine,

phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl, or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

X' represent O, N and $C(R^{17})$ where R^{17} represents hydrogen and alkyl radicals;

Y' and Y" independently represent O, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocycle;

R^6 represents hydrogen and alkyl radicals;

R^{30}, R^{31} and R^{32} independently represent radicals as defined for R^1, or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical; and

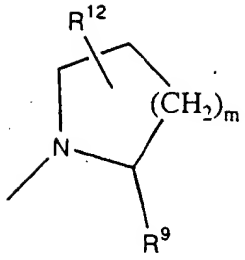
R^{33} and R^{34} independently represent radicals as defined for R^3, or R^{33} and R^{34} together with X' represent cycloalkyl, aryl, heterocyclyl and heteroaryl radicals, provided that when X' is O, R^{34} is absent.

Claim 39 (withdrawn)

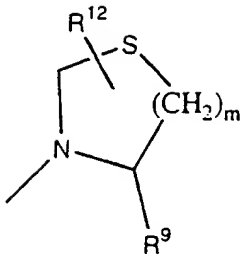
39. A compound of Claim 38 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic; and R^6 represents hydrogen and alkyl radicals.

Claim 40 (withdrawn)

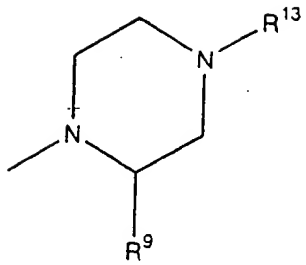
40. A compound of Claim 39 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



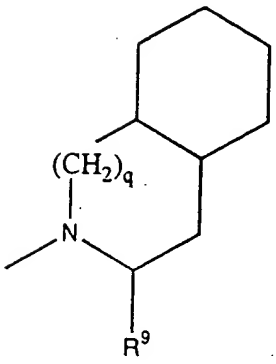
(A)



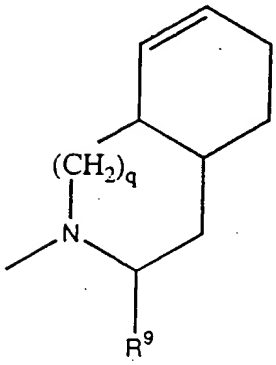
(B)



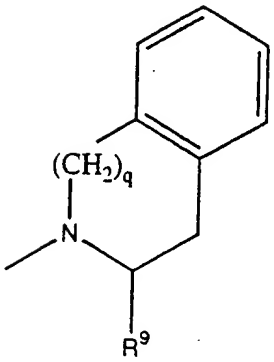
(C)



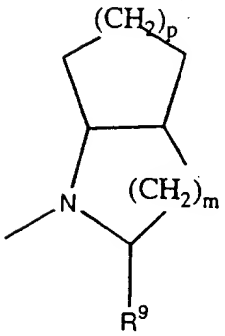
(D)



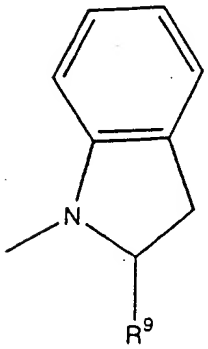
(E)



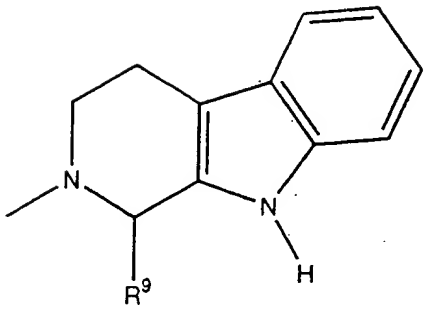
(F)



(G)



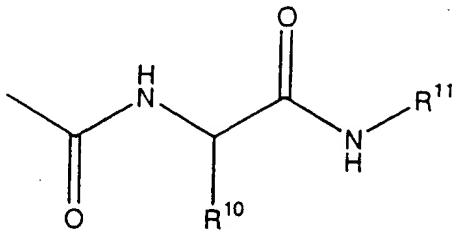
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^5 represents hydrogen and alkyl radicals.

Claim 41 (withdrawn)

41. A compound of Claim 38 where Y' and Y" are oxygen.

Claim 42 (withdrawn)

42. A compound of Claim 38 where R^2 is arylthioalkyl.

Claim 43 (withdrawn)

43. A compound of Claim 38 where t is 0.

Claim 44 (withdrawn)

44. A compound of Claim 39 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

Claim 45 (withdrawn)

45. A compound of Claim 38 where X' is oxygen.

Claim 46 (withdrawn)

46. A compound of Claim 38 where X' is nitrogen.

Claim 47 (withdrawn)

47. A compound of Claim 38 where R^{33} and R^{34} are hydrogen, alkyl, cycloalkyl, aralkyl or haloalkyl.

Claim 48 (withdrawn)

48. A compound of Claim 38 where R^{33} and R^{34} taken together with the nitrogen to which they are attached form a heterocyclic ring.

Claim 49 (withdrawn)

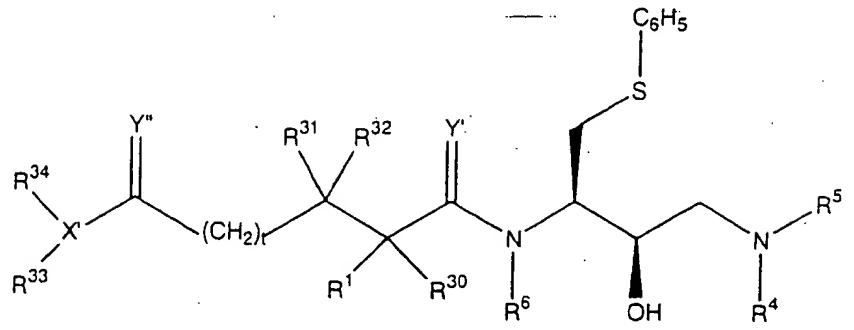
49. A compound of Claim 40 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

Claim 50 (withdrawn)

50. A compound of Claim 38 where R^1, R^{30}, R^{31}, R^{32} are hydrogen or alkyl.

Claim 51 (withdrawn)

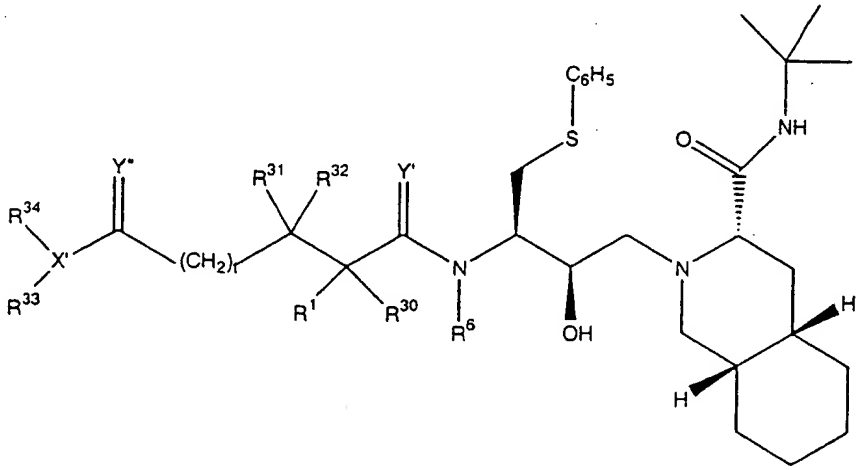
51. A compound of Claim 38 represented by the Formula



wherein R^1, R^6, Y', Y", R^4, R^5, R^{30}, R^{31}, R^{32}, R^{33}, R^{34} and t are as described herein.

Claim 52 (withdrawn)

52. A compound of Claim 40 represented by the formula



wherein R, R', R^1, R^6 and Y' are as described herein.

Claim 53 (withdrawn)

53. A pharmaceutical composition comprising a compound of Claim 38 and a pharmaceutical carrier.

Claim 54 (withdrawn)

54. A pharmaceutical composition comprising a compound of Claim 38 and a pharmaceutical carriers.

Claim 55 (withdrawn)

55. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 38.

Claim 56 (withdrawn) 56. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 38.

Claim 57 (withdrawn)

57. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 38.

Claim 58 (withdrawn)

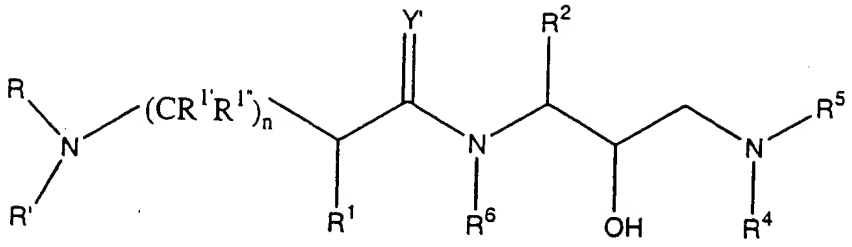
58. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 38.

Claim 59 (withdrawn)

59. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 38 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

Claim 60 (withdrawn)

60. A compound represented by the formula:



(Formula IV)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

R represents hydrogen, alkoxycarbonyl, aryloxycarbonylalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbanoyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocycloxycarbonyl, heteroaralkoxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroarylcarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aralkylaminoalkylcarbonyl, aminoalkanoyl,

aminocarbonyl, aminocarbonylalkyl, alkylaminoalkylcarbonyl, and mono- and disubstituted aminocarbonyl and aminoalkanoyl radicals wherein the substituents are selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of disubstituted aminoalkanoyl, said substituents along with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl radical;

R' represents radicals defined for R^3, or R and R' together with the nitrogen to which they are attached form a heterocycloalkyl or heteroaryl radical;

n represents 1 or 2;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(0)NH_2$, $-C(0)NHCH_3$, $-C(0)N(CH_3)_2$, $-CH_2C(0)NHCH_3$, $-CH_2C(0)N(CH_3)_2$, alkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl, haloalkyl, alkoxyalkyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl, or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocylic moiety;

R^6 represents hydrogen and alkyl radicals.

Claim 61 (withdrawn)

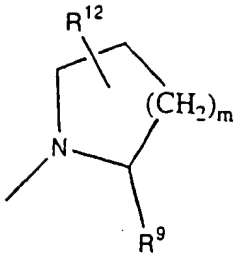
61. A compound of Claim 60 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic.

Claim 62 (withdrawn)

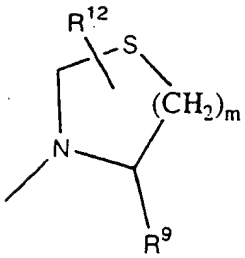
62. A compound of Claim 60 where n is 1.

Claim 63(withdrawn)

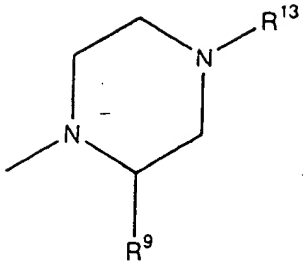
63. A compound of Claim 60 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



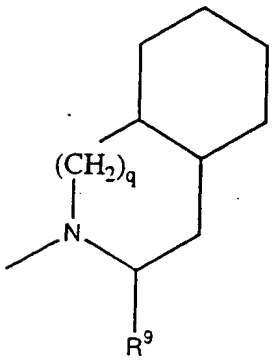
(A)



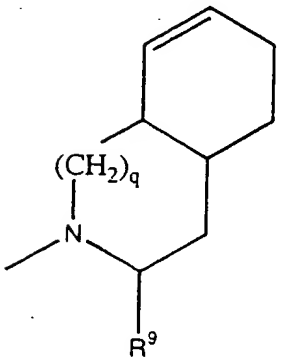
(B)



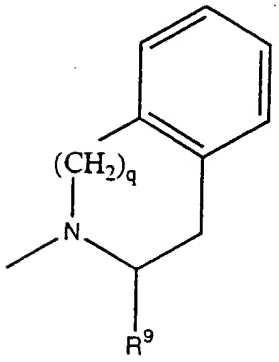
(C)



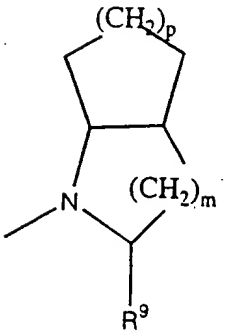
(D)



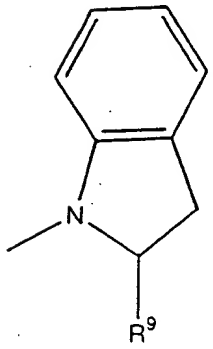
(E)



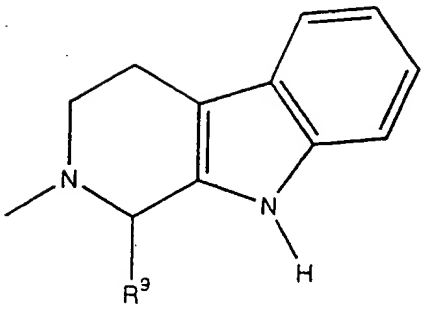
(F)



(G)



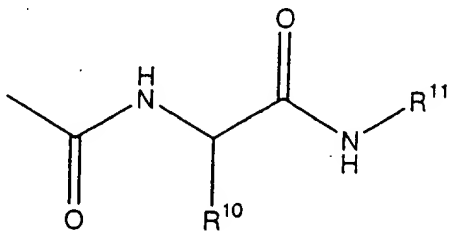
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^5 represents hydrogen and alkyl radicals.

Claim 64 (withdrawn)

64. A compound of Claim 60 where Y' is oxygen.

Claim 65 (withdrawn)

65. A compound of Claim 60 where R^2 is arylthioalkyl.

Claim 66 (withdrawn)

66. A compound of Claim 61 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

Claim 67 (withdrawn)

67. A compound of Claim 60 where R is hydrogen, alkoxycarbonyl, arylalkylcarbonyl, heterocyclecarbonyl, aminoalkanoyl, mono-substituted aminoalkanoyl, di-substituted aminoalkanoyl.

Claim 68 (withdrawn)

68. A compound of Claim 62 where $R^{1'}$ and $R^{1''}$ are hydrogen.

Claim 69 (withdrawn)

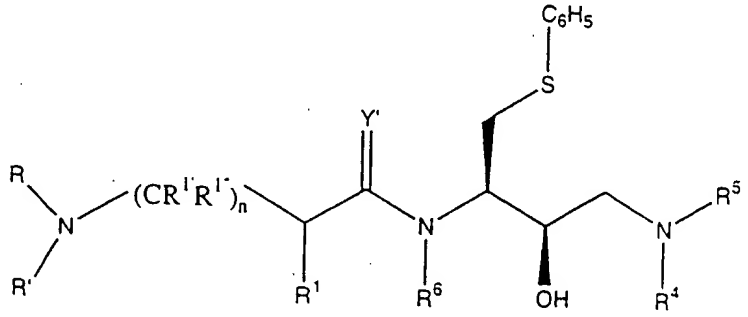
69. A compound of Claim 60 where R' is hydrogen.

Claim 70 (withdrawn)

70. A compound of Claim 60 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

Claim 71 (withdrawn)

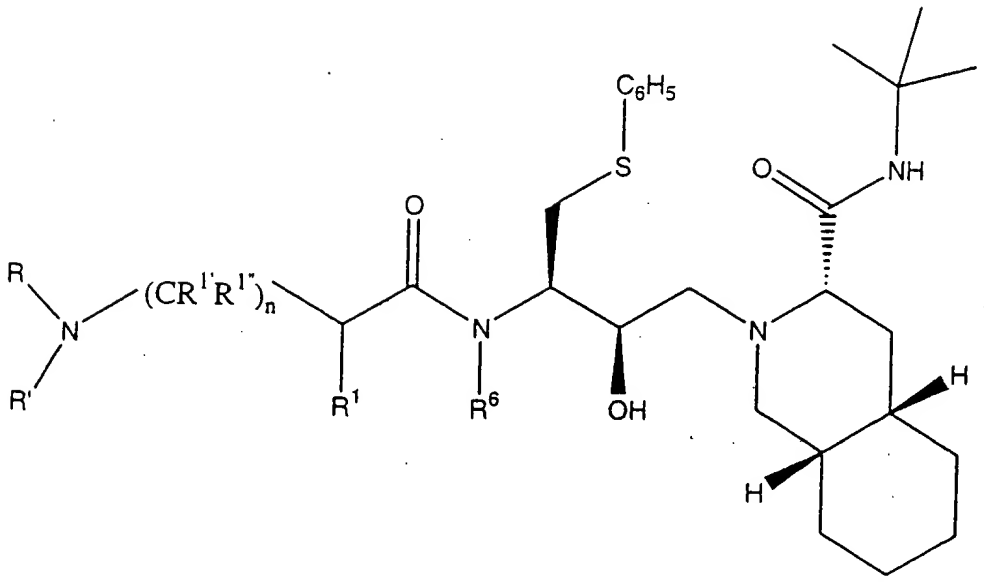
71. A compound of Claim 60 represented by the formula



wherein R, R', R^1, $R^{1'}$, $R^{1''}$, R^6, R^4, R^5 and Y' are as described herein.

Claim 72 (withdrawn)

72. A compound of Claim 63 represented by the formula



wherein R, R', R^1, $R^{1'}$, $R^{1''}$, R^6 and Y' are as described herein.

Claim 73 (withdrawn)

73. A pharmaceutical composition comprising a compound of Claim 60 and a pharmaceutical carrier.

Claim 74 (withdrawn)

74. A pharmaceutical composition comprising a compound of Claim 60 and pharmaceutical carriers.

Claim 75 (withdrawn)

75. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 60.

Claim 76 (withdrawn)

76. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 60.

Claim 77 (withdrawn)

77. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 60.

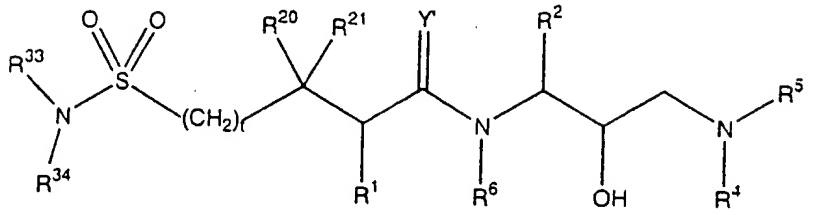
Claim 78 (withdrawn) 78. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 60.

Claim 79 (withdrawn)

79. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 60 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

Claim 80 (withdrawn)

80. A compound represented by the formula:



(Formula IIa)

or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-C(0)NH_2$, $-C(0)NHCH_3$, $-C(0)N(CH_3)_2$, $-CH_2C(0)NHCH_3$, $-CH_2C(0)N(CH_3)_2$, alkyl, alkylthioalkyl, thioalkyl and the corresponding sulfoxide and sulfone derivatives thereof, alkenyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from the group consisting of asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, alanine, phenylalanine, ornithine, histidine, norleucine, glutamine, valine, threonine, allo-threonine, serine, aspartic acid and beta-cyano alanine side chains;

R^2 represents alkylthioalkyl, cycloalkylthioalkyl or arylthioalkyl radicals, which radicals are optionally substituted with a substituent selected from the group consisting of $-NO_2$, $-OR^{15}$, $-SR^{15}$, and halogen radicals, wherein R^{15} represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y' represents O, S and NR^3;

R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocycle;

R^6 represents hydrogen and alkyl radicals;

R^{33} and R^{34} independently represent radicals as defined for R^3, or R^{33} and R^{34} together with the nitrogen to which they are attached form heterocyclyl and heteroaryl radicals;

and R^{20} and R^{21} represent radicals as defined for R^1.

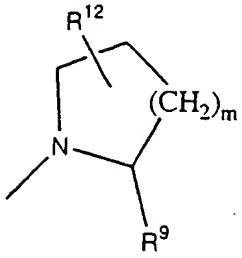
Claim 81 (withdrawn)

81. A compound of Claim 80 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a N-heterocyclic moiety containing 5, 6 or 7 members when monocyclic, 5, 6 or 7 members in a ring with 1, 2 or 3 members in a bridge when a bridged

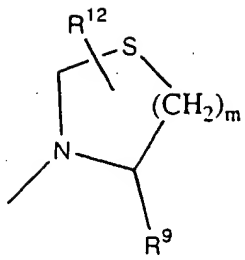
monocyclic, 11, 12 or 13 members when bicyclic, and 11 to 16 members when tricyclic; and R^6 represents hydrogen and alkyl radicals.

Claim 82 (withdrawn)

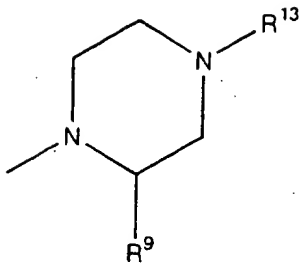
82. A compound of Claim 80 where R^4 and R^5 together with the nitrogen atom to which they are bonded form a N-heterocyclic moiety selected from the group consisting of formulae (A) through and including (J)



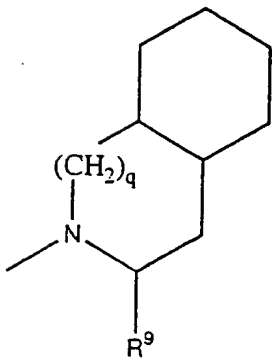
(A)



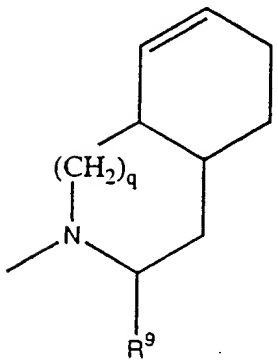
(B)



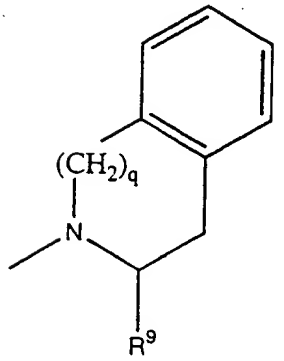
(C)



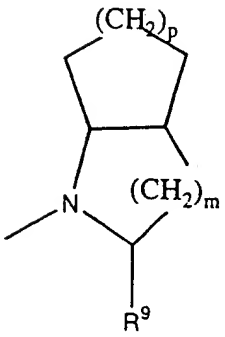
(D)



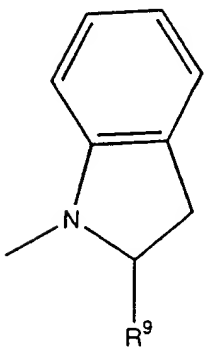
(E)



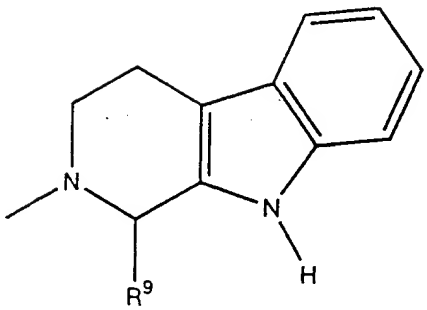
(F)



(G)



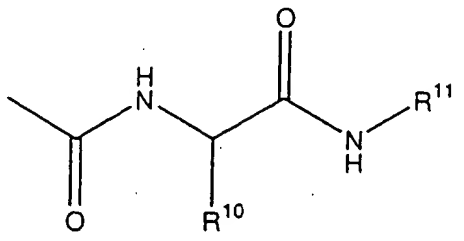
(H)



(J)

wherein:

R^9 represents hydrogen, alkyl, alkoxycarbonyl, monoalkylcarbamoyl, monoaralkylcarbamoyl, monoarylcarbamoyl or a group of the formula:



R^{10} and R^{11} each represents alkyl;

R^{12} represents hydrogen, hydroxy, alkoxycarbonylamino or acylamino;

R^{13} represents hydrogen, alkyl, aryl, alkoxycarbonyl or acyl;

m is 1, 2, 3, or 4;

p is 1 or 2;

q is 0, 1 or 2; and R^6 represents hydrogen and alkyl radicals.

Claim 83 (withdrawn)

83. A compound of Claim 80 where Y' is oxygen.

Claim 84 (withdrawn)

84. A compound of Claim 80 where R^2 is arylthioalkyl.

Claim 85 (withdrawn)

85. A compound of Claim 80 where t is 0.

Claim 86 (withdrawn)

86. A compound of Claim 81 where R^4 and R^5 together with the nitrogen atom to which they are bonded represent a bicyclic N-heterocyclic moiety.

Claim 87 (withdrawn)

87. A compound of Claim 80 where R^{33} and R^{34} are hydrogen, alkyl, cycloalkyl, aralkyl or haloalkyl.

Claim 88 (withdrawn)

88. A compound of Claim 80 where R^{33} and R^{34} taken together with the nitrogen to which they are attached form a heterocyclic ring.

Claim 89 (withdawn)

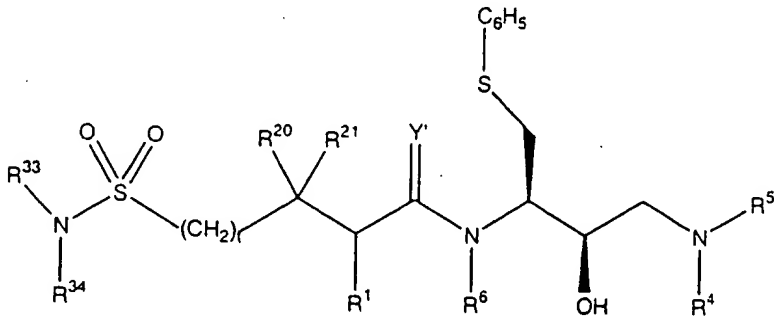
89. A compound of Claim 80 where R^1 is hydrogen, alkyl, thioalkyl, alkylthioalkyl, alkenyl, alkynyl and cycloalkyl.

Claim 90 (withdrawn)

90. A compound of Claim 80 where R^{20} and R^{21} are hydrogen or alkyl.

Claim 91 (withdrawn)

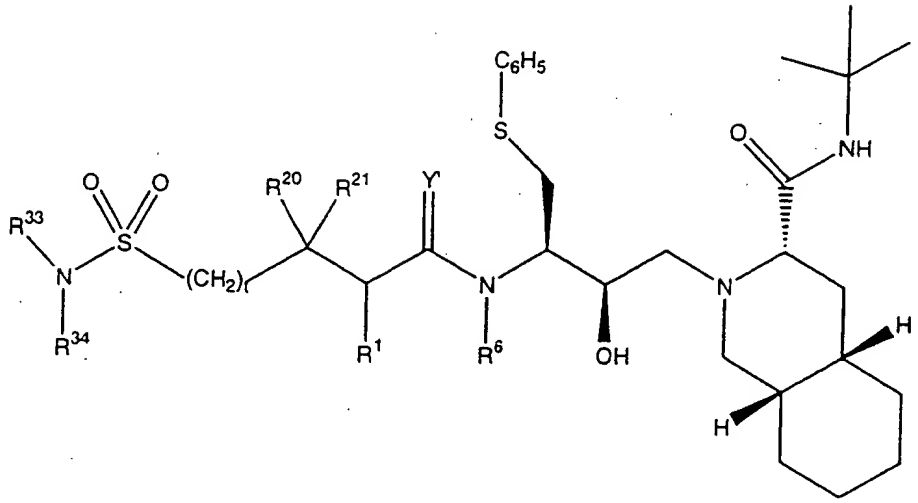
91. A compound of Claim 80 represented by the Formula



wherein R^1, R^6, R^4, R^5, R^{20}, R^{21}, R^{33}, R^{34}, t and Y' are as described herein.

Claim 92 (withdrawn)

92. A compound of Claim 82 represented by the formula



wherein R^1, R^6, R^{20}, R^{21}, R^{33}, R^{34}, t and Y' are as described herein.

Claim 93 (withdrawn)

93. A pharmaceutical composition comprising a compound of Claim 80 and a pharmaceutical carrier.

Claim 94 (withdrawn)

94. A pharmaceutical composition comprising a compound of Claim 80 and a pharmaceutical carriers.

Claim 95 (withrawn)

95. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a compound of Claim 80.

Claim 96 (withdrawn)

96. Method of treating a retroviral infection comprising administering a pharmaceutical composition of a compound of Claim 80.

Claim 97 (withdrawn)

97. Method of treating HIV infection comprising administering a pharmaceutical composition of a compound of Claim 80.

Claim 98 (withdrawn)

98. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 80.

Claim 99 (withrdawn)

99. Method of treating AIDS comprising administering a pharmaceutical composition of a compound of Claim 80 in combination with other drugs for the treatment of AIDS or the symptoms of AIDS.

REMARKS

The Office Action

The Office Action makes final a second restriction requirement entered in paper no. 9.

Claims 19-37 have been examined, claims 1-18 and 38-99 having been withdrawn as non-elected. As set forth at page 3 of the Office Action, claims 19-37 have been examined "as they read on a compound of formula II where t is 0 to 2, R20 represents radicals as defined for R1 except amino acid side chains claimed, R21 represents radicals as defined for R1 except the amino acid side chains claimed, R2 is as claimed, R' represents radicals defined for R3 except heterocycloalkyl, heteroaryl, heterocycloalkylalkyl and heteroaralkyl radicals, R5 is H, alkyl, R4 and R5 come together with nitrogen to which they are attached to form a hydrogenated isoquinoline ring which includes D, E, F when Q is q."

Claim 33 stands rejected in part under 35 U.S.C. § 112, first paragraph, because a skilled practitioner would not know how to use the claimed invention. The claim is said not to be supported by a specific asserted utility or a well-established utility. Inhibiting a retroviral protease is said to be a mechanism, and the disease being treated is not stated.

This rejection had been withdrawn in the Office Action dated January 14, 2003.

Claim 34 is discussed, and the following comments are set forth. However, there is no rejection stated at this point in the Office Action. Rather, the rejection seems to be set forth below. The Office Action notes that the art is unpredictable. Therefore, even though the level of skill is high, treatment of retroviruses is unpredictable. Because the specification is said not to give any guidance for the effect of the compound of claim 34 (inasmuch as claim 34 is a method claim, it is likely that the comment should be directed to the compound of claim 19, and will be so construed) on treatment of retroviruses other than HIV, the claim would require undue experimentation. Viral treatment is said to be virus-specific, "[s]o the treatment of HIV by the

compound claimed in claim 6 and 7 [sic] does not predict the treatment of another virus." Inasmuch as the specification is said to be lacking good direction, the Office Action states that "it is not seen where the instant **claims** are enabled by the instant specification." [emphasis added]. Applicants trust that this rejection is directed to rejection of claim 34 only, as no other **claims** are specifically identified.

Claim 37 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter applicants regard as the invention. The Office Action questions which other drugs applicants are claiming in view of the phrase "in combination with other drugs" in the claim.

Claims 19-37, in part, stand rejected under 35 U.S.C. § 112, first paragraph, "because the specification, does not reasonably provide enablement for the radicals R3 equaling all heterocyclic rings and R4 and R5 coming together with the nitrogen atom to which they are bonded to form all nitrogen heterocyclic rings."

Claims 19-37 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Although the Office Action admits that there are a "few examples of prodrugs, esters, and derivatives depicted in the specification," this showing is said not to be sufficient.

Claim 34 stands rejected under 35 U.S.C. § 112, first paragraph, as not enabling for a method of treating all retroviruses, or for treating HIV. The Office Action repeats much of the material already described above, including confusing reference to claim 6 (treatment of retrovirus) and claim 7 (treatment of HIV).

Claims 29 and 30 stand rejected as indefinite because various R moieties are not specifically defined.

Claims 31 and 32 are said to be substantial duplicates.

Claims 30-32 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Claim 30 includes a definition of R^4 and R^5 more inclusive than the structural formula illustrated. Claims 31 and 32 are said to be indefinite "because they are pharmaceutical composition claims tha [sic] do not make any reference to the dosage of the composition being administered."

Claims 19-37 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hornback, US 5,480,887, in view of Dressman, US 5,484,926. Hornback is said to have 'generically disclosed' the claimed compounds (reference is made to CAS 124:289512, a 2-sheet Chemical Abstracts summary of the 29-page patent), and Dressman allegedly teaches equivalence between what Hornback discloses and the claimed invention.

The Amendments

The amendments merely clarify the claims by including the definitions of moieties, rather than merely referring to the definitions. In claim 30, R^4 and R^5 have been deleted as not required in view of the nature of the ring formation of the right terminus moiety set forth in the structural formula.

These amendments are supported by the claims as filed and throughout the specification. These amendments add no new matter to the application, and Applicants earnestly solicit entry thereof.

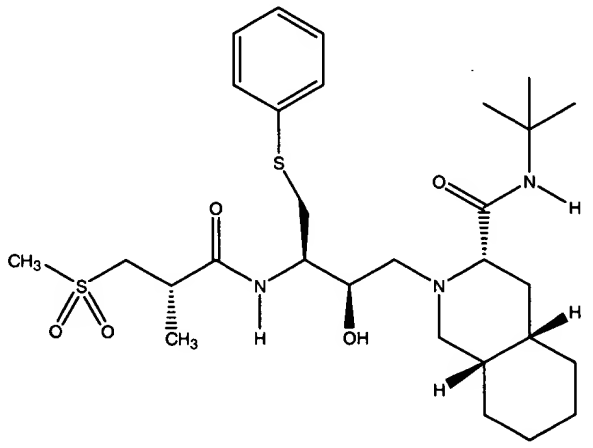
I. Status of the Restriction Requirements

To date, one original restriction requirement and three additional restriction requirements were imposed on Applicants' originally filed claims 1-99. In response to the original restriction requirement, Applicants elected a species and identified the subgroup of claims 19-37 as reading thereon. Subsequently, three additional restriction requirements have been entered, each of which purports to be based on a "liberal interpretation of the doctrine of legal and chemical equivalence". For detailed reasons given below, Applicants respectfully submit that these three additional restriction requirements not only fail to set forth a restriction group encompassing Applicants' elected species (Issue III), but also are procedurally and substantively improper (Issue IV).

A. The Original Restriction Requirement (June 5, 2001)

The Office Action dated June 5, 2001, imposed a Restriction Requirement on originally-filed claims 1-99. Applicants were required under 35 U.S.C. § 121 to elect a single disclosed species. In response, Applicants elected the species of Example 22, set forth at page 147, lines 16-23.

The elected species has the structure



and is within the scope of Formula II of claim 19, wherein R′ is methyl (alkyl), t is 0, R^{20} is H (hydrogen), R^{21} is H (hydrogen), R^1 is methyl (alkyl), Y′ is O (oxygen), R^6 is H (hydrogen), R^2 is phenylthiomethyl (arylthioalkyl), and R^4 and R^5 together with the nitrogen to which they are bonded represent an N-heterocycle[1]. Applicants also identified claims 19-37 as reading on this compound and its use.

B. The First *Additional* Restriction Requirement (December 4, 2001)

The following Office Action, dated December 4, 2001, noted the election of the above species and further stated, "The Examiner will now use this species as a reference point to create a natural genus based on a liberal interpretation of the doctrine of legal and chemical equivalence and restriction will be required under 35 U.S.C. § 121." The Examiner identified allegedly separate inventions, directed to compounds of Formula I, as follows:

> I. Claims 19-37, drawn to the compound of formula I where R1 is all moieties not containing a heterocyclic ring, t is 2, R2 is arylthioalkyl, a method of treating classified in class 546, subclass 146 and class 514 sublcass 307.
>
> II. Claims 1-99, drawn to the compounds of formula I where R1, R20, and R21, R21, and R2 are all other moieties not covered in group I, and a method of treating classified in various classes, subclasses.

In response to this further restriction requirement, Applicants respectfully submitted that it was impossible to select a group for prosecution because the substituents t, R^{20}, and R^{21} do not appear in Formula I. Furthermore, the elected species is not a compound of Formula I. Applicants also pointed out that, even if the identification of Formula I was a typographical error and the restriction was intended to be based on Formula II, the groups would still make no sense because

[1] Specifically, the N-heterocycle corresponds to the structure D on page 22 of the specification, wherein q is 1 and R^9 is t-butylcarbamoyl (a monoalkylcarbamoyl, described on page 23, lines 5-8).

t cannot be 2 in Formula II. Because the proposed restriction groups are not found in the application, Applicants could not select a group satisfying the restriction requirement. Nevertheless, to at least satisfy the practice requirement that a group be selected in response to a restriction, Applicants selected that group (whatever it might be) in which the Examiner intended the species of Example 22 to fall.

C. The Second *Additional* Restriction Requirement (July 16, 2002), Made Final

In response to Applicants comments, the following Office Action, dated July 16, 2002, modified the restriction as follows:

> Genus I, drawn to claims 19-37, concerns a compound of Formula II in claim 19 where t is 0 to 1, R1=R20=R21 are all moieties claimed except the amino acid side chains claimed, R2 is as claimed, R'=R3 is all moieties claimed except heterocycloalkly, heteroaryl, heterocycloalkylalkyl, and heteroaralkyl radicals, R6 is H, alkyl, R4 and R5 come together with the nitrogen to which they are attached to form a hydrogenated isoquinolinyl which would include rings D, E, and F when Q is 1.
>
> The elected species of example 22 now reads on the elected invention.

In their response to this second additional restriction requirement, Applicants again submitted that the elected species is not a member of the genus to which the Examiner sought to limit prosecution. In particular, the elected species requires, *inter alia*, that R' be methyl and R^{20} and R^{21} be H. Thus, the elected species cannot be a member of a genus in which "R' = R^{20} = R^{21}".

Without addressing these arguments, the Office Action dated January 14, 2003 rendered the restriction requirement **final**. The Examiner asserted that

> The elected species does fit into the natural genus of group I because R3 of formula II can equal alkyl, t can equal 1, R1 can equal alkyl, R20 and R21 can equal alkyl, Y1 can equal oxygen, R6 can equal H, R2 can equal alkylthioaryl, and R4 and R5 can form a nitrogen heterocyclic ring.

However, Applicants could not understand the significance of this statement because, as explained above, in the elected species, R^3 is **not** alkyl[2], t is **not** 1, and R^{20} and R^{21} are **not** alkyl, and R^2 is **not** alkylthioaryl[3]. Applicants therefore sought to understand the nature of the first and second additional restriction requirements in a personal interview.

D. Finality of the Second *Additional* Restriction Requirement Withdrawn

In the personal interview between the Examiner and Applicants' undersigned representatives on July 3, 2003, Applicants again submitted that the requirement to restrict claims 19-37 to compounds of the "natural genus" wherein "R^1=R^{20}=R^{21}" was inconsistent with the elected species. Applicants' representatives also pointed out that the Examiner's assertions regarding the possibilities for R^3, t, R^{20}, R^{21}, and R^2 in the Final Office Action were, for reasons given above, not a basis for asserting that the elected species falls into the "natural genus" of Group I.

In the interview, the Examiner agreed that t is 0, not 1, in the elected species. The Examiner also agreed that R^3, although recited in the restriction requirement, does not appear in the structural Formula II set forth in claim 19. The Examiner further agreed that it was appropriate to withdraw the finality of the outstanding Office Action. Applicants' representatives requested clarification insofar as the Examiner mischaracterized the elected

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[2] R^3 is in fact nonexistent in the elected species, because Y' is O (oxygen) and not a radical of the formula NR^3. In an Examiner interview on July 3, 2003, Applicants' representatives suggested that the Examiner might have meant that R' can be methyl, since R' represents radicals as defined for R^3 and R^3 can be methyl. Applicants requested clarification in the record on this point (*i.e.*, how R' of the elected species fits the restriction group) in the written interview summary, but none was made.

[3] In the elected species, R^2 is phenylthiomethyl, which is an arylthioalkyl group, signifying attachment of the alkyl (not aryl) part of this group to the core molecule. Applicants pointed out this nomenclature issue in the July 3, 2003 Examiner interview, requesting clarification in the record on this point (*i.e.*, how R^2 of the elected species fits the restriction group) in the written interview summary, but none was made.

species and its relationship to the Formula II.

E. Withdrawn Restriction Requirement Lasted Only One Business Day; Third *Additional* Restriction Requirement Entered

In subsequent telephone conferences on July 8, 2003 with Applicants' representatives, the Examiner stated that the finality of the Office Action would not be withdrawn, because, even though the restriction requirement entered at Paper No. 9 was confusing and poorly phrased, it encompassed the elected species (the compound of Example 22). Applicants again disagreed that the requirement "R^1=R^{20}=R^{21}" encompassed the elected species, at least because R^1 does not equal R^{20} or R^{21}. Thereafter, the Examiner issued an Interview Summary of both the July 3, 2003 and July 8, 2003, personal and telephonic interviews, respectively, asserting the propriety of the second *additional* restriction requirement (July 16, 2002). In this interview summary, the Examiner "clarified" what was actually meant by the original restriction requirement, which had already been made final well before this point. However, this "clarification" is in fact merely the imposition of yet another restriction requirement, namely, a third *additional* restriction requirement.

Based on the above, Applicants submit that the proposed Group I of the restriction requirement imposed on December 14, 2001, and modified on July 16, 2002, was not drawn to subject matter reading on the elected species. Therefore, rendering this restriction requirement final in the January 14, 2003, Office Action was improper.

II. The Present Restriction Requirement

The Office Action now makes final the additional restriction requirement allegedly first described on July 16, 2002. However, the Office Action at page 2, repeats the erroneous characterization of Applicants' elected compound, provided in the January 14, 2003 Office Action. In particular, the Office Action asserts

> [t]he elected species does fit into the natural genus of group I because R3 of formula II can equal alkyl, t can equal 1, R1 can equal alkyl, R20 and R21 can equal alkyl, Y1 can equal oxygen, R6 can equal H, R2 can equal alkylthioaryl, and R4 and R5 can form a nitrogen heterocyclic ring.

Therefore, for the same reasons given under subheading "C" above, the Examiner is again describing a restriction group that does not embrace the elected species. Namely, in the elected species, R^3 is **not** alkyl, t is **not** 1, and R^{20} and R^{21} are **not** alkyl, and R^2 is **not** alkylthioaryl.

Moreover, the statement at page 3 of the Office Action, as follows, indicates clearly and unambiguously that the claims are being examined in areas to which they do not extend.

> Claims 19-37 are examined below as they read on a compound of formula II where t is 0 to 2, R20 represents radicals as defined for R1 except amino acid side chains claimed, R21 represents radicals as defined for R1 except the amino acid side chains claimed, R2 is as claimed, R' represents radicals defined for R3 except heterocycloalkyl, heteroaryl, heterocycloalkylalkyl and heteroaralkyl radicals, R5 is H, alkyl, R4 and R5 come together with nitrogen to which they are attached to form a hydrogenated isoquinoline ring which includes D, E, F when Q is q.

Applicants respectfully submit that this scope of examination is outside the scope of claims 19-37. First, *t cannot equal 2* in the claims being examined. Second, *R^5 cannot be H or alkyl.* Inasmuch as R^6 is not mentioned at all, perhaps the recitation of "H, alkyl" was intended to apply to R^6, but given the repeated changes in the restriction requirements, Applicants are not at all sure. Finally, Applicants do not understand the statement "when Q is q."

This restriction requirement has been made final. Applicants separately petition for review of this requirement. Applicants have elected the species of Example 22, within the scope of

Formula II of claim 19. Applicants respectfully submit that Applicants are entitled to examination of the species, and then, if the species is found allowable, other species in the claims are to be examined. It is not clear that the elected species has been examined. What has been examined appears to be beyond the scope of the claims.

Further, if the Examiner seeks to further restrict, after an election of species, it seems that Applicant should be afforded the opportunity to select the subject matter to be examined, after identification of the options set forth by the Examiner. Applicants respectfully submit that this is how restriction requirements work — the Examiner identifies the Groups for restriction, articulates reasons for the requirement, and the Applicants make the selection. This procedure has not been followed in this prosecution.

Applicants submit that the Restriction Requirement imposed in the December 4, 2001, Office Action is in direct contrast to well-established examination principles set forth MPEP § 803.02, relating to restriction practice for Markush claims. Importantly, this restriction requirement is a <u>further</u> requirement. In the June 5, 2001, Office Action, Applicants first elected a species (*i.e.*, the compound of Example 22 on page 147, lines 16-23 of the specification) for examination, and identified claims 19-37 as reading thereon[4]. The Examiner then made a <u>further</u> restriction requirement based on "a liberal interpretation of the doctrine of legal and chemical equivalence."

Applicants respectfully submit the further restriction requirement is directly contrary to MPEP § 803.02. In particular, after Applicants complied with the election-of-species requirement, they were entitled to <u>full examination</u> on the merits of claims 19-37, reading on the elected species. According to the above-cited MPEP section, in Markush claim practice,

[4] Importantly, after the election of species, claims 19-37 were rejected under 35 U.S.C § 102(b) and this rejection was overcome.

> ...the examiner may require a provisional election of a single species prior to examination on the merits. ...Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. (emphasis added).
>
> . . . .
>
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a *non-elected species*, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration.

Furthermore, the MPEP requires full examination of claims 19-37, reading on the elected species, regardless of whether these claims encompass independent inventions. Specifically, MPEP § 803.02 provides

> If the members of the Markush group are ...so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. (emphasis added).

The fact that the proposed restriction would have split the claims into only two groups *(i.e.*, the "natural genus" and everything else) negates any of the Examiner's contentions as to the burden of examining the claims 19-37 in their entirety.

Furthermore, MPEP § 803.02 states, "[I]t is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention." (emphasis added). Unity of invention is based on well-settled judicial precedent[5]. For example, the MPEP cites *In re Harnisch* and *Ex parte Hozumi*. 206 U.S.P.Q. 300 (C.C.P.A.

[5] In the Examiner interview on July 3, 2003, Applicants' representatives clarified to the Examiner that the term "unity of invention" as it applies to U.S. restriction practice is not the same as that used under the PCT articles to restrict inventions.

1980) and 3 U.S.P.Q.2d 1059 (Bd. Pat. App. & Int. 1984). In *Harnisch*, the Court of Customs and Patent Appeals rejected the imposition of a restriction requirement in a Markush-type claim where all of the compounds had a single use, and thus had unity of invention. Likewise, in *Hozumi*, the Board of Patent Appeals and Interferences (hereinafter "Board") reversed a rejection of a Markush-type claim, where the compounds were core structures having plural diverse pendant moieties.

Other decisions reinforce the proposition that unity of invention is based on a common utility. For example, in *In re Jones*, the Court of Customs and Patent Appeals reversed the Board's 'improper Markush group' rejection precisely because the claimed compounds had a common function. 162 F.2d 479, 74 U.S.P.Q. 149 (C.C.P.A.1947). In *Ex parte Dahlen*, 42 U.S.P.Q. 208 (Bd. App. 1938), the Board permitted claims to compounds having a common core with pendant widely-varying side chains, because the claimed compounds had a community of properties.

Based on the above decisions, claims 19-37 have unity of invention, because these claims embrace a single inventive concept. The compounds of claim 19 are retroviral protease inhibitors. These have a single common core and pendant moieties, as set forth in the definitions of R', t, R^{20}, R^{21}, R^1, Y', R^6, R^2, R^4, and R^5. No matter which combination of pendant moieties is selected, the resulting compound is a retroviral protease inhibitor. Such compounds may also have other uses, but all are retroviral protease inhibitors. To restrict claims 19-37 to any scope less than their full scope is contrary to established precedent and MPEP guidance.

Based on the above, Applicants submit that the proposed Group I of the restriction requirement imposed on December 14, 2001, and modified on July 16, 2002, was not drawn to

subject matter reading on the elected species. Therefore, rendering this restriction requirement final in the January 14, 2003, Office Action was improper.

In summary, Applicants elected a species, in response the restriction requirement imposed in the Office Action dated June 5, 2001. Established procedures of MPEP § 803.02 require full examination of claims reading on the elected species. For these reasons, Applicants respectfully submit that the Examiner's requirement to further restrict these claims to specified Markush members is improper.

III. Claim 33 Is Supported By A Utility

Claim 33 stands rejected under 35 U.S.C. § 112, first paragraph, as not supported by a utility, and thus is said not to teach a skilled practitioner how to use the invention. Applicants respectfully traverse this rejection. "[I]nhibiting a retroviral protease" is a specific utility. As set forth in the application at pages 154-161, HIV protease is inhibited by compounds of claim 33, as illustrated by both enzyme and CEM cell assays. Further, it is well known to skilled practitioners that inhibition of retroviral protease is effective in treating a number of diseases, including HIV, respiratory syncitial, virus, hepadnavirus, and cytomegalo virus. Indeed, treatment of such diseases, and others, by inhibiting retroviral protease is disclosed in US Patent No. 5,756,533, which is incorporated by reference into the application.

The Federal Circuit has made it abundantly clear that inhibition of an enzyme, together with knowledge in the art that the enzyme inhibition is related to treatment of a disease state, satisfies the utility requirement under 35 U.S.C. § 112, first paragraph. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985). In *Cross*, the application at issue disclosed a practical utility for the claimed imidazole derivatives, namely, the inhibition of thromboxane synthetase *in*

vitro, together with the stated utility of treating inflammation. The Federal Circuit accepted this utility, where, as Applicants have done here, a utility is disclosed and supported with *in vitro* data. Therefore, Applicants respectfully submit that a utility is described in the specification in a manner that instructs a skilled practitioner how to use the claimed invention of claim 33.

The citation in the Office Action of *In re Fouche* and *In re Wands* is unavailing. Applicants respectfully submit that the application fully provides the information required to inform a skilled practitioner how to use the invention. In particular, the application fully satisfies the *Wands* factors cited by the Examiner. Applicants respectfully submit that the predictability of inhibiting retroviral protease, which is what is claimed, is well established in the specification for compounds of claim 33 at pages 154-161. The enzyme and CEM cell assays show the effectiveness. Dosage and other treatment information are set forth at pages 163-169. Applicants respectfully submit the effectiveness of other compounds of the claims is reasonably supported by the illustrated effective inhibiting retroviral protease in the Examples. In this regard, Applicants respectfully submit that treatment of specific diseases, to which the Examiner has directed the argument relating to the *Wands* factors, is not a relevant enquiry. Applicants respectfully traverse this rejection

IV. Claim 34 Is Enabled

The Office Action states that the "nature of the invention is claim 34 is the treating of HIV infection and retroviral infection." Claim 34 is directed to treatment of a retroviral infection.

The reasons set forth in this rejection are disjointed, with part of the discussion at the beginning of the Office Action without actual identification of the rejection. The rejection, set forth later in the Office Action, mentions claims 6 and 7. Applicants simply do not understand

this reference. Claims 6 and 7, which are withdrawn from consideration herein, are directed to compounds. They are not directed to treatment.

As this rejection is understood by Applicants, Applicants respectfully traverse this rejection. The Office Action asserts that no treatment regimen would be accepted on its face, and thus appears to suggest that Applicants must test every compound claimed. This clearly is not the standard for enablement. The Office Action specifically mentions the inability to predict the results of the administration of the compound of claim 6.

The Office Action also states that there is absolutely no predictability in this art, but identifies nothing to support this statement. Even if it is known that no compound is effective against all retroviruses, that statement does not render the claim not enabled. Rather, the question is whether the skilled practitioner would be able to practice the invention without undue experimentation with a reasonable expectation of success. Applicants respectfully traverse this rejection. Applicants respectfully submit that the Office Action suggests that certainty is demanded when only a reasonable expectation of success is required. On this point, the Federal Circuit has made it clear that the showing of efficacy through clinical trials, while necessary to obtain FDA approval,

> is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In re Brana, 51 F.3d. 1560, 1568 (Fed. Cir. 1995) (emphasis added). As such, Applicants' claim 34, directed to a method of treatment, is enabled without the need to demonstrate clinical efficacy, as the Office Action apparently requires.

The Office Action alleges that there is no guidance about the effect of the claimed compounds on the treatment of retroviruses other than HIV. Because HIV is one such virus, this teaching supports the claim. Further, the skill and knowledge of the practitioner must be considered. Thus, information in the prior art can provide such information. Indeed, the specification sets forth clear guidance with regard to other retroviral infections.

Retroviral infections are well known and have a definite meaning to the ordinary skilled artisan. In particular, retroviral infections arise from HIV and other lentiviruses such as HIV-2, respiratory syncitial virus, hepadnavirus, picornavirus, and cytomegalovirus. Not only are retroviral infections well known, the above retroviruses and others are disclosed in U.S. Patent No. 5,756,533, incorporated into the application by reference. The '533 patent also discloses the treatment of retroviral infections by inhibiting retroviral protease.

The Office Action asserts that undue experimentation would be required to use the invention. However, this assertion is unsupported and is specifically contradicted by the repeated assertions that the skill level in the art is high. Any experimentation is not undue. Either the compound works on the target retroviral infection, or it does not. Contrary to the assertion in the Office Action, there is no need for exhaustive search for 'which retroviruses can be treated.'

The Office Action appears to suggest a lack of enablement because a route of administration is not specified. The Office Action asks "Is the route of administration *in vitro* or *in vivo*?" Applicants respectfully submit that the method of claim 34 applies to both *in vitro* and

in vivo retroviral protease inhibition. The specification clearly shows the potent *in vitro* enzyme inhibitory activity of the compounds tested in Table 1 at pages 160-161. Regarding the relationship between the need for *in vivo* testing and the enablement requirement of 35 U.S.C. § 112, first paragraph, the Federal Circuit has held that

> Of course, it is possible that some compounds active *in vitro* may not be active *in vivo*. But as our predecessor court in Nelson explained, a "rigorous correlation" need not be shown in order to establish practical utility; "reasonable correlation" suffices.

Fujikawa v. Wattanasin, 93 F.3d 1559, 1565 (Fed. Cir. 1996). In this regard, the correlation between *in vitro* inhibition of retroviral protease and the treatment of a number of disease states, including HIV, respiratory syncitial, virus, hepadnavirus, and cytomegalo virus, is well known in the art. Indeed, treatment of such diseases, and others, by inhibiting retroviral protease is disclosed in US Patent No. 5,756,533, which is incorporated by reference into the application.

If the above information is not somehow not satisfactory, Applicants note that there is ample additional known evidence linking protease inhibition with AIDS treatment. For example, several companies have had protease inhibitor compounds for treating HIV infection/AIDS in clinical trials in the United States. These include Vertex Pharmaceuticals (VX-478), Agouron Pharmaceuticals (AG-1343), Merck (L-735,523), Roche (Saquinavri or Ro 31-0959), and Abbott Laboratories (ABT-538). In this regard, *Biotechnology Newswatch* (February 5, 1996) reported that the use of a protease inhibitor available from Merck caused HIV infection to decrease to an undetectable level. The plasma HIV RNA fell below detectable levels (less than 500 copies of the virus) in 41% of the patients in Indivavir monotherapy for 12 weeks. Furthermore, the Wall Street Journal (March 15, 1996) reported U.S. Food and Drug Administration (FDA) approval of Merck's Crixivan shortly after approval of Abbott's Norvir for the treatment of AIDS. Both of these drugs

are HIV protease inhibitors. If necessary, Applicants can provide copies of the above-mentioned articles at the Examiner's request.

V. The Identity of the "Other Drugs" in Claim 37 Is Clear

The Office action asserts that claim 37, in part, is indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention. The question is "Which other drugs is the applicant claiming?"

The phrase in question is not simply "in combination with other drugs." Rather, the phrase is "in combination with other drugs for the treatment of AIDS or the symptoms of AIDS." Applicants respectfully submit that the meaning of "drugs for the treatment of AIDS or the symptoms of AIDS" is not only known in the art but is also set forth in the specification at page 167, line 10 to page 168, line 10. In contrast to what the Office Action contends, the claim is not rendered indefinite merely because it encompasses "a vast array of drugs with varying structures." It is well established that breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971) and MPEP § 2173.04.

During a personal interview on July 3, 2003, the Examiner suggested to Applicants' undersigned representatives that this rejection would stand simply because the chemical formulas of these other drugs were not disclosed and claimed. Applicants respectfully submit, however, that it is unnecessary to specifically identify the chemical formulas of these drugs. A patent specification is not required to be as detailed as a production blueprint. Some experimentation and exercise of judgment is to be expected in adapting an invention to a particular use. *Douglas v. U.S.*, 510 F.2d 364, 366 (Ct. Cl. 1975). In this case, the invention of claim 37 is directed to the particular use of combination therapy with the claimed compounds.

VI. Claims 19-37 Are Enabled

The Office Action identifies the breadth of the definitions of the R^3 and R^4/R^5 moieties. As R^3 is not present in the compound of claim 19, Applicants are confused about this rejection. However, as R^1 is present on the claimed compound, and the R^1 moiety has the same scope as the R^3 moiety, perhaps this is the moiety the Office Action intended to identify.

Claims 19-37 stand rejected under 35 U.S.C. § 112, first paragraph, for lacking sufficient enablement for the making and using compounds within the scope of these claims. The Office Action contends that the specification does not enable the scope of the claimed (1) R^3 and R′ heterocyclic moieties and (2) N-heterocyclic moieties formed by R^4 and R^5, together with the nitrogen atom to which they are bonded. Applicants respectfully traverse this rejection.

It is well established that Applicants are entitled to a presumption of enablement. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Specifically,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (emphasis added).

In re Marzocchi and Horton, 169 USPQ 367, 370 (C.C.P.A. 1971).

The Office Action fails to provide a single technical reason or a hint of objective evidence to rebut the presumption of enablement relating to use of the claimed invention. Instead, the Office Action states "only one compound falling within the elected restriction group were [*sic*] only tested for enzyme inhibition, antiviral activity, and cell toxicity, where the R^3 is methyl, and the R^4 and R^5 come together to form saturated isoquinoline." This one observation is offered as allegedly bearing on the 5th, 6th, and 7th of the so-called *Wands* factors.

The compound within falling within the scope of claim 19 that is exemplified, tested, and proven to be a potent retroviral protease inhibitor in Table 1 on page 160 (1st entry) contains a saturated isoquinoline R^4/R^5 structure, which is a nitrogen-containing heterocyclic ring. In any event, the number of compounds tested has absolutely no bearing on the 5th *Wands* factor, which is the level of predictability *in the art.* Furthermore, the Office Action's contention that "[t]he applicant does not test the whole breadth of compounds encompassing all of the moieties that these particular radicals can be" is misguided. It is manifest that no working examples are required to satisfy enablement, let alone examples directed to every claimed radical group. *In re Fouche*, 169 USPQ 429, 434 (C.C.P.A. 1971). Nevertheless, the high chemical and biological activity and low toxicity of the compounds tested according to the enzyme and CEM cell assays are as described and reported at 154, line 14 to page 161, line 3.

The Office Action provides no objective evidence showing that even a single claimed compound would not possess inhibitory activity. Instead, the Office Action states summarily that the *Wands* factor on undue experimentation is satisfied merely because multiple radical groups are claimed.

During the July 3, 2003, personal interview, the Examiner suggested a lack of enablement could be found because potency may be affected when these radicals are interchanged. (This assertion is, of course, contrary to the bold assertion made in support of the obviousness rejection that substitution of known effective moieties yields effective compounds). However, the key to a rejection based on lack of enablement is whether *undue* experimentation is required. In the claimed invention, the compounds inhibit retroviral protease. Undue experimentation is not required to identify an inhibitory compound. Because the compounds necessarily do not have identical potency (*Fouche*, 169 U.S.P.Q. at 434), it likely will be necessary to adjust dosage.

However, such dosage adjustments are *not* considered *undue* experimentation. *US v. Telectronics*, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Rather, dose/response studies are within the skill of a practitioner, and do not constitute undue experimentation. *Telectronics*, 8 U.S.P.Q. 2d at 1224.

The Office Action fails to rebut the presumption of enablement of a skilled practitioner's ability to make the claimed invention. The Office Action provides neither rationale nor evidence that a person skilled in the art would have doubted that any of the claimed compounds could have been routinely made according to procedures detailed in the specification, or that any such compound would possesses the asserted utility as a retroviral protease inhibitor. Indeed, numerous methods of making the compounds are described at page 25, line 4, to page 154, line 12, of the specification. Methods of using the invention are described at page 161, line 8, to page 168, line 9.

Nothing in the record suggests that undue experimentation would have been required to (i) synthesize compounds within the claims, and (ii) test the compounds for protease inhibition activity as described in the specification with a reasonable expectation that the tested compound would exhibit some degree of the asserted activity.

In summary, Applicants respectfully submit that the Examiner's subjective feeling about the number of examples is not a well-founded legal position. Rather, the Office Action improperly tries to shift the burden to Applicants to demonstrate that the claims are enabled, without first providing the legally required, objective evidence to question the asserted enablement of the claimed compounds. The rejection therefore completely ignores the presumption of enablement to which Applicants are entitled. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

VII. Claims 19-37 Comply with the Written Description Requirement

Claim 19 includes the phrase "or a pharmaceutically acceptable salt, prodrug or ester thereof." No claim is directed to 'derivatives,' so Applicants do not understand this portion of the rejection.

Skilled practitioners recognize pharmaceutically acceptable salts, prodrugs, and esters. This is not a point that requires significant disclosure in this specification. For example, skilled practitioners recognize that any of the pharmaceutically acceptable salts disclosed at pages 161 through 163 of the application can be utilized. Similarly, prodrugs are well-known in the art. Skilled practitioners recognize that an ester can be made at virtually any hydroxyl moiety of the compound, such as the one on the claimed compound. Applicants respectfully traverse this rejection.

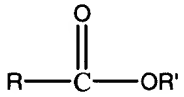
As is readily understood by one of ordinary skill, the term "prodrug" refers to a form of the compound that becomes pharmaceutically active under physiological conditions (*i.e.*, in the body). It is accepted that a "prodrug" is a pharmaceutical compound that has been chemically modified. A prodrug may be biologically inactive at its site of action, but in this case it is degraded or modified by one or more enzymatic or other *in vivo* processes to the parent, bioactive form. Generally, a prodrug has a different pharmacokinetic profile than the parent compound such that, for example, it is more easily absorbed across the mucosal epithelium, it has better salt formation or solubility, and/or it has better systemic stability (*e.g.*, an increased half-life).

Those skilled in the art recognize prodrugs as chemically-modified pharmaceutical compounds that include (1) terminal ester or amide derivatives that are susceptible to being

cleaved by esterases or lipases, (2) terminal peptide derivatives that may be recognized by specific or nonspecific proteases, (3) derivatives that cause accumulation at a site of action through membrane selection, and (4) forms having various combinations of these modifications.

Conventional procedures for the selection and preparation of prodrugs are described, for example, by H. Bundgaard, *Design of Prodrugs* (1985) and by Sinkula, A. A. and Yalkowsky, S. H.; Rationale for Design of Biologically Reversible Drug Derivatives: Prodrugs, *Journal of Pharmaceutical Sciences*, 64(2), 181-210 (1975). If necessary, Applicants can provide copies of these references at the Examiner's request.

Likewise, Applicants submit that the term "ester" is well known in the art. According to standard chemical nomenclature, an "ester" is a compound having the chemical linkage:



Thus, for example, a methyl ester derivative is obtained when R′ = CH_3. Esters are as well defined as oxides, ketones, carboxylic acids, halides, thiols, and other chemical classes. The preparation of esters is well-documented in standard chemistry textbooks. See, *e.g.*, English *et al.*, Principles of Organic Chemistry, 2nd Ed., McGraw-Hill Book Company, Inc. 245-7 (1956), describing carbonyl transfer to the oxygen of a parent molecule to yield its ester derivative. Again, Applicants can provide copies of these references at the Examiner's request.

Ester derivatives of anti-HIV compounds in particular are also known and are described, for example, in U.S. Patent No. 5,003,072, which details the esterification of pendant hydroxyl groups.

For the above reasons, one skilled in the art would understand what prodrugs and esters could be used in practicing the claimed invention and how such prodrugs and esters are prepared. The written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied.

VIII. Claims 29 and 30 Are Definite

Claims 29 and 30 have been amended to clarify any potential confusion. Applicants respectfully traverse this rejection. Claim 30 also has been amended to eliminate any definition of R^4/R^5 that is inconsistent with the structural formula illustrated.

IX. Claims 31 and 32 Are Not Substantial Duplicates

Claim 31 is directed to a pharmaceutical composition comprising a pharmaceutical carrier, whereas claim 32 requires pharmaceutical carriers. As is clear, therefore, a composition comprising a single carrier would infringe claim 31, but not claim 32. Thus, the claims are not substantial duplicates.

X. Claims 31 and 32 Are Definite

Claims 31 and 32 are said to be indefinite because they are composition claims that do not identify the dosage of the compound administered. Applicants respectfully traverse this rejection. As is clear from the specification, the compound of claim 19 can be administered in many ways (intravenously or orally, for example). Skilled practitioners recognize that the manner of administration has a significant effect on the dosage level. The pharmaceutical compositions claimed are not limited to one mode of administration, and therefore admit of many concentrations, as set forth in the specification. The claims are definite.

XI. Claims 19-37 Are In Condition For Allowance

Claims 19-37 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hornback, US 5,480,887, in view of Dressman, US 5,484,926. Hornback is said to have 'generically disclosed' the claimed compounds (reference is made to CAS 124:289512, a 2-sheet Chemical Abstracts summary of the patent), and Dressman allegedly teaches equivalence between what Hornback discloses and the claimed invention. Despite the unpredictability of the art argued in rejection of

the claims under 35 U.S.C. § 112, substitution of one moiety for another now is said to be perfectly predictable. To the extent such substitution is made, it is only with improper hindsight reconstruction.

Applicants respectfully traverse this rejection. First, neither the Chemical Abstracts Summary nor the full text of the Hornback patent disclose the claimed compounds, generically or otherwise. Note that the R moiety of Hornback must disclose the entire left end of the claimed molecule from the carbon bonded to the Y' moiety. Thus, considering the CAS document, one sees an N molecule in the spine of the compound where R^{21} and R^{22} are attached to a carbon molecule in the claimed invention. If Hornback's R is Q1, that clearly does not yield a compound that generically or otherwise discloses the claimed compound.

The Office Action also claims that Hornback's claim 1 generically discloses the claimed compound. Simple inspection shows that Hornback's R moiety cannot yield the claimed compound.

The proposed combination with Dressman adds nothing relevant to the disclosure of Hornback. The arguments in the Office Action relate only to the *right* terminus of the claimed compound. Thus, Dressman adds nothing that satisfies the shortcomings of Hornback.

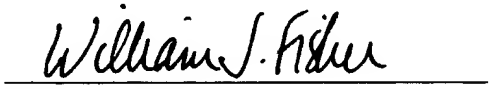
Applicants respectfully traverse this rejection.

CONCLUSION

Accordingly, for all of the above reasons, all pending claims of this application are believed to be in condition for allowance, and such action is respectfully requested.

Respectfully submitted,

Date: August 30, 2003

By: 

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	Examiner: Robinson, B.
Richard A. MUELLER *et al.*	)	
	)	Group Art Unit: 1625
Serial No.: 09/625,384	)	
	)	Atty Dkt No.: 101765.00054
Filed: July 26, 2000	)	(3128/1)

For: RETROVIRAL PROTEASE INHIBITORS

REQUEST FOR RECONSIDERATION OR, IN THE ALTERNATIVE, PETITION TO THE COMMISSIONER UNDER 37 C.F.R. § 1.181(a)(1)

U.S. Patent and Trademark Office
220 20th Street S.
Customer Window
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

In response to the Office action dated March 29, 2004, Applicants request reconsideration of the Examiner's FINAL requirement for restriction or in the alternative, petition the Commissioner under 37 C.F.R. § 1.181(a)(1) to review the Examiner's FINAL requirement to **(i)** elect a restriction group drawn to subject matter that *does not read on the elected species* and **(ii)** *further* restrict, after Applicants' election of species and before initiation of any examination of this elected species, the already-elected subject matter of claims 19-37.

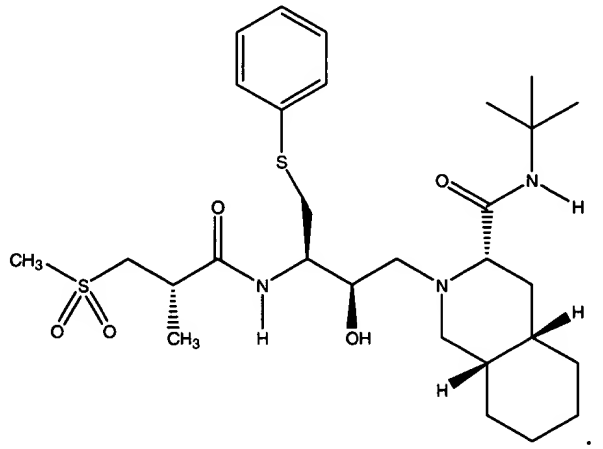
If a fee is required for this submission, for consideration of the alternative petition, or to consider this submission timely, please charge our Deposit Account 19-0733.

STATEMENT OF FACTS

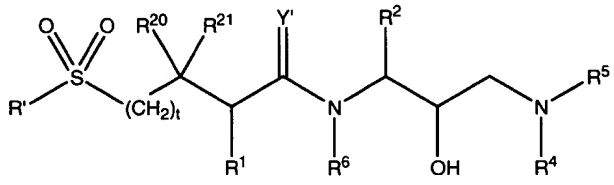
A. The Original Restriction Requirement (June 5, 2001)

The Office Action dated June 5, 2001, imposed a Restriction Requirement on originally-filed claims 1-99. Applicants were required under 35 U.S.C. § 121 to elect a single disclosed species. In response, Applicants elected the species of Example 22, set forth at page 147, lines 16-23.

The elected species has the structure



This compound is within the scope of claim 19, which is directed to a compound of Formula II:



In terms of the pendent moieties R', t, R^{20}, R^{21}, Y', and R^1–R^6 as recited in claim 19, the elected species is a compound of Formula II wherein R' is methyl (alkyl), t is 0, R^{20} is H (hydrogen), R^{21} is H (hydrogen), R^1 is methyl (alkyl), Y' is O (oxygen), R^6 is H (hydrogen), R^2 is phenylthiomethyl (arylthioalkyl), and R^4 and R^5 together with the nitrogen to which they are bonded represent an N-

heterocycle[1]. In their response to the restriction requirement, Applicants identified claims 19-37 as reading on this compound and its use.

B. The First *Additional* Restriction Requirement (December 4, 2001)

The following Office Action, dated December 4, 2001, noted the election of the above species and further stated, "The Examiner will now use this species as a reference point to create a natural genus based on a liberal interpretation of the doctrine of legal and chemical equivalence and restriction will be required under 35 U.S.C. § 121." The Examiner identified allegedly separate inventions, directed to compounds of Formula I, as follows:

> I. Claims 19-37, drawn to the compound of formula I where R1 is all moieties not containing a heterocyclic ring, t is 2, R2 is arylthioalkyl, a method of treating classified in class 546, subclass 146 and class 514 sublcass 307.
>
> II. Claims 1-99, drawn to the compounds of formula I where R1, R20, and R21, R21, and R2 are all other moieties not covered in group I, and a method of treating classified in various classes, subclasses.

In response to this further restriction requirement, Applicants respectfully submitted that it was impossible to select a group for prosecution because the substituents t, R^{20}, and R^{21} do not appear in Formula I. Furthermore, the elected species is not a compound of Formula I. Applicants also pointed out that, even if the identification of Formula I was a typographical error and the restriction was intended to be based on Formula II, the groups would still make no sense because t cannot be 2 in Formula II. Because the proposed restriction groups are not found in the application,

[1] Specifically, the N-heterocycle corresponds to the structure D on page 22 of the specification, wherein q is 1 and R^9 is t-butylcarbamoyl (a monoalkylcarbamoyl, described on page 23, lines 5-8).

Applicants could not select a group satisfying the restriction requirement. Nevertheless, to at least satisfy the practice requirement that a group be selected in response to a restriction, Applicants selected that group (whatever it might be) in which the Examiner intended the species of Example 22 to fall.

C. The Second *Additional* Restriction Requirement (July 16, 2002), Made Final

In response to Applicants' comments, the following Office Action, dated July 16, 2002, modified the restriction as follows:

> Genus I, drawn to claims 19-37, concerns a compound of Formula II in claim 19 where t is 0 to 1, R1=R20=R21 are all moieties claimed except the amino acid side chains claimed, R2 is as claimed, R'=R3 is all moieties claimed except heterocycloalkly, heteroaryl, heterocycloalkylalkyl, and heteroaralkyl radicals, R6 is H, alkyl, R4 and R5 come together with the nitrogen to which they are attached to form a hydrogenated isoquinolinyl which would include rings D, E, and F when Q is 1.
>
> The elected species of example 22 now reads on the elected invention.

In their response to this second additional restriction requirement, Applicants again submitted that the elected species is not a member of the genus to which the Examiner sought to limit prosecution. In particular, the elected species requires, *inter alia*, that R' be methyl and R^{20} and R^{21} be H. Thus, the elected species cannot be a member of a genus in which "$R' = R^{20} = R^{21}$".

Without addressing these arguments, the Office Action dated January 14, 2003 rendered the restriction requirement **final**. The Examiner asserted that

> The elected species does fit into the natural genus of group I because R3 of formula II can equal alkyl, t can equal 1, R1 can equal alkyl, R20 and R21 can equal alkyl, Y1 can equal oxygen, R6 can equal H, R2 can equal alkylthioaryl, and R4 and R5 can form a nitrogen heterocyclic ring.

However, Applicants could not understand the significance of this statement because, as explained above, in the elected species, R^3 is **not** alkyl[2], t is **not** 1, and R^{20} and R^{21} are **not** alkyl, and R^2 is **not** alkylthioaryl[3]. Applicants therefore sought to understand the nature of the first and second additional restriction requirements in a personal interview.

D. Finality of the Second *Additional* Restriction Requirement Withdrawn

In the personal interview between the Examiner and Applicants' undersigned representatives on July 3, 2003, Applicants again submitted that the requirement to restrict claims 19-37 to compounds of the "natural genus" wherein "R^1=R^{20}=R^{21}" was inconsistent with the elected species. Applicants' representatives also pointed out that the Examiner's assertions regarding the possibilities for R^3, t, R^{20}, R^{21}, and R^2 in the Final Office Action were, for reasons given above, not a basis for asserting that the elected species falls into the "natural genus" of Group I.

In the interview, the Examiner agreed that t is 0, not 1, in the elected species. The Examiner also agreed that R^3, although recited in the restriction requirement, does not appear in the structural Formula II set forth in claim 19. The Examiner further agreed that it was appropriate to withdraw

---

[2] R^3 is in fact nonexistent in the elected species, because Y' is O (oxygen) and not a radical of the formula NR^3. In an Examiner interview on July 3, 2003, Applicants' representatives suggested that the Examiner might have meant that R' can be methyl, since R' represents radicals as defined for R^3 and R^3 can be methyl. Applicants requested clarification in the record on this point (*i.e.*, how R' of the elected species fits the restriction group) in the written interview summary, but none was made.

[3] In the elected species, R^2 is phenylthiomethyl, which is an arylthioalkyl group, signifying attachment of the alkyl (not aryl) part of this group to the core molecule. Applicants pointed out this nomenclature issue in the July 3, 2003 Examiner interview, requesting clarification in the record on this point (*i.e.*, how R^2 of the elected species fits the restriction group) in the written interview summary, but none was made.

the finality of the outstanding Office Action. Applicants' representatives requested clarification insofar as the Examiner mischaracterized the elected species and its relationship to the Formula II.

E. Withdrawn Restriction Requirement Lasted Only One Business Day; Third *Additional* Restriction Requirement Entered

In subsequent telephone conferences on July 8, 2003 with Applicants' representatives, the Examiner stated that the finality of the Office Action would not be withdrawn, because, even though the restriction requirement entered at Paper No. 9 was confusing and poorly phrased, it encompassed the elected species (the compound of Example 22). Applicants again disagreed that the requirement "$R^1=R^{20}=R^{21}$" encompassed the elected species, at least because R^1 does not equal R^{20} or R^{21}. Thereafter, the Examiner issued an Interview Summary of both the July 3, 2003 and July 8, 2003, personal and telephonic interviews, respectively, asserting the propriety of the second *additional* restriction requirement (July 16, 2002). In this interview summary, the Examiner "clarified" what was actually meant by the original restriction requirement, which had already been made final well before this point. However, this "clarification" is in fact merely the imposition of yet another restriction requirement, namely, a third *additional* restriction requirement.

F. Office Action Dated March 29, 2004

In the most recent Office Action dated March 29, 2004, the Examiner again asserts

> [t]he elected species does fit into the natural genus of group I because R3 of formula II can equal alkyl, t can equal 1, R1 can equal alkyl, R20 and R21 can equal alkyl, Y1 can equal oxygen, R6 can equal H, R2 can equal alkylthioaryl, and R4 and R5 can form a nitrogen heterocyclic ring.

Thus, for the same reasons given under subheading "C" above, the Examiner is again describing a restriction group that does not embrace the elected species. Namely, in the elected species, R^3 is **not** alkyl, t is **not** 1, and R^{20} and R^{21} are **not** alkyl, and R^2 is **not** alkylthioaryl.

Moreover, the statement at page 3 of the Office Action, as follows, indicates clearly and unambiguously that the claims are being examined in areas to which they do not extend.

> Claims 19-37 are examined below as they read on a compound of formula II where t is 0 to 2, R20 represents radicals as defined for R1 except amino acid side chains claimed, R21 represents radicals as defined for R1 except the amino acid side chains claimed, R2 is as claimed, R' represents radicals defined for R3 except heterocycloalkyl, heteroaryl, heterocycloalkylalkyl and heteroaralkyl radicals, R5 is H, alkyl, R4 and R5 come together with nitrogen to which they are attached to form a hydrogenated isoquinoline ring which includes D, E, F when Q is q.

Applicants respectfully submit that this scope of examination is outside the scope of claims 19-37. First, *t cannot equal 2* in the claims being examined. Second, *R^5 cannot be H or alkyl.* Inasmuch as R^6 is not mentioned at all, perhaps the recitation of "H, alkyl" was intended to apply to R^6, but given the repeated changes in the restriction requirements, Applicants are not at all sure. Finally, Applicants do not understand the statement "when Q is q."

1st Ground for Petition

Failure to Specify a Restriction Group Embracing the Elected Species

After Applicants complied with the election of species requirement in the June 5, 2001 Office Action, *none* of the three additional proposed restriction requirements set forth a restriction group encompassing Applicants' elected species. Thus, it is not clear that the elected species has been

examined. Furthermore, what has been examined appears to be beyond the scope of the claims.

As stated in the facts above, one original restriction requirement and three additional restriction requirements to date were imposed on Applicants' originally filed claims 1-99. In response to the original restriction requirement, Applicants elected a species and identified the subgroup of claims 19-37 as reading thereon. Subsequently, three additional restriction requirements have been entered, each of which purports to be based on a "liberal interpretation of the doctrine of legal and chemical equivalence". In view of the facts given above, Applicants respectfully submit that these three additional restriction requirements fail to set forth a restriction group encompassing Applicants' elected species.

Therefore, rendering any of the above-noted restriction requirements FINAL is improper. Reconsideration and withdrawal of the restriction requirement on this ground is therefore respectfully requested.

2nd Ground for Petition

Improper *Further* Restriction, before Examination of the Elected Species

After electing a species for examination, Applicants are entitled to examination on the merits of claims 19-37 (which read on that species) in their entirety. Applicants have elected the species of Example 22, within the scope of Formula II of claim 19. Applicants respectfully submit that Applicants are entitled to examination of the species, and then, if the species is found allowable, other species in the claims are to be examined.

Further, if the Examiner seeks to further restrict, after an election of species, it seems that Applicant should be afforded the opportunity to select the subject matter to be examined, after identification of the options set forth by the Examiner. Applicants respectfully submit that this is how restriction requirements work — the Examiner identifies the Groups for restriction, articulates reasons for the requirement, and the Applicants make the selection. This procedure has not been followed in this prosecution.

Applicants submit that the Restriction Requirement imposed in the December 4, 2001, Office Action, is in direct contrast to well-established examination principles set forth MPEP § 803.02, relating to restriction practice for Markush claims. Importantly, this restriction requirement is a further requirement. In the June 5, 2001, Office Action, Applicants first elected a species (*i.e.*, the compound of Example 22 on page 147, lines 16-23 of the specification) for examination, and

identified claims 19-37 as reading thereon[4]. The Examiner then made this further restriction requirement based on "a liberal interpretation of the doctrine of legal and chemical equivalence."

Applicants respectfully submit the further restriction requirement is directly contrary to MPEP § 803.02. In particular, after Applicants complied with the election-of-species requirement, they were entitled to full examination on the merits of claims 19-37, reading on the elected species. According to the above-cited MPEP section, in Markush claim practice,

> ...the examiner may require a provisional election of a single species prior to examination on the merits. ...Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. (emphasis added).
>
> . . . .
>
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a *non-elected species*, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration.

Furthermore, the MPEP requires full examination of claims 19-37, reading on the elected species, regardless of whether these claims encompass independent inventions. Specifically, MPEP § 803.02 provides

> If the members of the Markush group are ...so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim

[4] Importantly, after the election of species, claims 19-37 were rejected under 35 U.S.C § 102(b) and this rejection was overcome.

> on the merits, even though they are directed to independent and distinct inventions. (emphasis added).

The fact that the proposed restriction would have split the claims into only two groups *(i.e.*, the "natural genus" and everything else) negates any of the Examiner's contentions as to the burden of examining the claims 19-37 in their entirety.

Furthermore, MPEP § 803.02 states, "[I]t is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention." (emphasis added). Unity of invention is based on well-settled judicial precedent[5]. For example, the MPEP cites *In re Harnisch* and *Ex parte Hozumi*. 206 U.S.P.Q. 300 (C.C.P.A. 1980) and 3 U.S.P.Q.2d 1059 (Bd. Pat. App. & Int. 1984). In *Harnisch*, the Court of Customs and Patent Appeals rejected the imposition of a restriction requirement in a Markush-type claim where all of the compounds had a single use, and thus had unity of invention. Likewise, in *Hozumi*, the Board of Patent Appeals and Interferences (hereinafter "Board") reversed a rejection of a Markush-type claim, where the compounds were core structures having plural diverse pendant moieties.

Other decisions reinforce the proposition that unity of invention is based on a common utility. For example, in *In re Jones*, the Court of Customs and Patent Appeals reversed the Board's 'improper Markush group' rejection precisely because the claimed compounds had a common function. 162 F.2d 479, 74 U.S.P.Q. 149 (C.C.P.A.1947). In *Ex parte Dahlen*, 42 U.S.P.Q. 208 (Bd. App. 1938), the Board permitted claims to compounds having a common core with pendant widely-

[5] In the Examiner interview on July 3, 2003, Applicants' representatives clarified that the term "unity of invention" as it applies to U.S. restriction practice is not the same as that used under the PCT articles to restrict inventions.

varying side chains, because the claimed compounds had a community of properties.

Based on the above decisions, claims 19-37 have unity of invention, because these claims embrace a single inventive concept. The compounds of claim 19 are retroviral protease inhibitors. These have a single common core and pendant moieties, as set forth in the definitions of R', t, R^{20}, R^{21}, R^1, Y', R^6, R^2, R^4, and R^5. No matter which combination of pendant moieties is selected, the resulting compound is a retroviral protease inhibitor. Such compounds may also have other uses, but all are retroviral protease inhibitors. To restrict claims 19-37 to any scope less than their full scope is contrary to established precedent and MPEP guidance.

In summary, Applicants elected a species, in response the restriction requirement imposed in the Office Action dated June 5, 2001. Established procedures of MPEP § 803.02 require full examination of claims reading on the elected species. For these reasons, Applicants respectfully submit that the Examiner's requirement to further restrict these claims to specified Markush members is improper.

Reconsideration and withdrawal of the restriction requirement on this alternate ground is therefore respectfully requested.

SUMMARY

For the above reasons, the finality of the restriction requirement is improper (i) because no restriction group is set forth embracing Applicants' elected species and (ii) the restriction requirement ignores well-established restriction practice.

WHEREFORE, Applicants respectfully petition withdrawal of the requirement for further restriction of the elected claims 19-37.

Respectfully submitted,

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